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Involving Minority and Underrepresented Women in Clinical Trials: The National Centers of Excellence in Women's Health

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ABSTRACT

Recent attention to reducing health disparities among population groups has focused on the need to include in clinical studies, especially clinical trials, participants who represent the diversity of the populations to which study results will be applied. While scientists generally applaud the goal of broadening the characteristics of participants in clinical trials, they are faced with multiple challenges as they seek to include historically underrepresented populations in their research. This article examines the historical and sociocultural context of participation by underrepresented groups, especially women and minorities, in clinical trials, identifies major barriers and challenges facing researchers, and suggests strategies for meeting these challenges. The article draws upon the experiences of the investigators affiliated with the National Centers of Excellence of Women's Health (CoEs).

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INTRODUCTION

One of the most critical challenges facing researchers in the health sciences today is the need to develop and test interventions that will improve the health of individuals, communities, and populations. These interventions are targeted at the prevention and treatment of existing and emerging diseases and conditions and the promotion of general health and well-being. Considerations of efficacy, acceptability, and cost are paramount. Although various types of basic and clinical studies are part of the program of research that leads to these interventions, the randomized controlled clinical trial has been generally accepted as the gold standard to test interventions. For many years, the predominant participant in clinical trials was a young adult, Caucasian male. Even in animal research, male rats predominantly were used. Reasons for the exclusion of females included the belief that data from men were cleaner because of the lack of interference from estrus or menstrual cycles and fear of inducing fetal deformities in pregnant subjects. Generally, the results of these trials were then applied to other individuals, including women, people of color, and younger and older persons. However, recent attention on reducing health disparities among population groups has focused on the need to include in clinical studies, especially clinical trials, participants who represent the diversity of the populations to which study results will be applied. This need is based on an emerging body of evidence of differential treatment and intervention effects in groups other than adult, Caucasian males.[1] Federal funding agencies, such as the National Institutes of Health (NIH), now require the participation of women, racial minorities, and children in the studies they support.

Scientists generally applaud the goal of broadening the characteristics of participants in clinical trials, but they are faced with multiple challenges as they seek to include historically underrepresented populations in their research. This report examines the historical and sociocultural contexts of participation by underrepresented groups, especially women and minorities, in clinical trials, identifies major barriers and challenges facing researchers, and suggests strategies for meeting these challenges. We draw upon the experiences of the investigators affiliated with the National Centers of Excellence of Women's Health (CoEs). These CoEs, located in academic medical centers across the United States and Puerto Rico, are made possible by funding from the Office on Women's Health (OWH) of the U.S. Department of Health and Human Services (DHHS). The CoEs are part of the national effort to reduce health disparities among specific population groups in the United States. They have as one of their goals the increased inclusion of historically underrepresented women in clinical trials. In this article, underrepresented groups include women in general and also specific subpopulations representing ethnic or racial groups, sexual minorities, and lower socioeconomic status.

HISTORICAL AND SOCIOCULTURAL CONTEXT

Clinical trials have evolved over the past 40–50 years to test the efficacy of medical interventions and medications. The randomized study design has been considered as the standard.[2] Participants and potential participants in clinical research are considered in need of protection from exploitation by researchers. Several historical events provide the foundation for this belief.

Experimentation on humans was a key issue during the Nuremberg Trials of the 1940s. Ethical approaches to medical research were codified in the Nuremberg Code and further elaborated in the 1964 Helsinki Declaration.[3–5] These documents declared the fundamental dignity of human beings involved as research subjects, including the principles of voluntary consent and risk-benefit evaluation. From this time through the 1970s, the prevailing principle guiding research in the United States was that research participants should be protected from exploitation. The 1966 NIH Policy and Procedure Order, requiring not only investigator but also peer review of research to assure the protection of human subjects, reflected this stance. During this time, the public regarded research as dangerous and of little value to individual participants.[6,7] The public disclosure and heated discussion regarding the government-sponsored Tuskegee Study, which from 1932 to 1972 continued observation without therapy of black men with syphilis, greatly exacerbated resentment and suspicion of the research

establishment by members of minority communities.[6,8] In 1974, Congress passed the National Research Act, which provided funding for the NIH and also established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This Commission further established protections for populations viewed as particularly vulnerable to exploitation or harm, including prisoners, the mentally disabled, and children.[5] In 1977, following the thalidomide tragedy and within the context of concern about fetal research, the Food and Drug Administration (FDA) established a policy excluding pregnant and potentially pregnant women from clinical trials.[5,6] In 1974, the NIH established the Office of Protection of Research Rights (OPRR), which provides regulatory guidance for and monitoring of research procedures that are reviewed at the local institutional level to ensure incorporation of community standards in terms of the objectives, design, hypotheses posed, and methods used.[5,7]

Within this historical and regulatory context, institutional review boards (IRBs) responsible for reviewing proposed research for protection of human subjects considered some populations of women as more vulnerable to potential harm from research and often placed additional requirements on investigators seeking the inclusion of women in research. Other populations were distrustful of researchers and justifiably hesitant to volunteer for clinical studies. As a result, investigators came to view inclusion of women and other underrepresented groups in clinical trials as challenging or problematic.

Current challenges to recruiting women and minorities to clinical studies must be viewed in the context of these historical and ongoing controversies about the ethics of clinical study designs and the ongoing exposure of studies that have exploited minority populations in the name of biomedical research. Ethical issues about study design have always existed in the biomedical sciences, and medical experimentation continues to be debated, for example, regarding the use of placebos.[9]

To understand and address the reluctance of minority and other underrepresented women to participate in research, it is important to also understand the sociocultural context of these women's experiences with experimentation and research. Their experiences often have been influenced by their vulnerability as a group that has not been equal in status and power to those conducting research and developing policies regarding experimentation. Experiences of racism coupled with sexism are powerful factors influencing women's decisions. Even when there is no malevolence intended, minority populations frequently have been faced with trying to understand the motives behind policies and procedures that take advantage of their disadvantaged position and lack of authority in traditional healthcare settings. Cultural differences also lead to miscommunication and misinterpretation of actions and motives, among both potential study participants and investigators.[10]

The Tuskegee syphilis study left many black Americans distrustful of the healthcare system generally and of medical research specifically. Recent media attention to the presidential apology for Tuskegee highlights the familiarity black Americans have with this study. For many, this project represents the epitome of how racism is reflected in medicine and medical research as it is in the general society. The premise of the Tuskegee experiment was based on assumptions of difference in the natural history of syphilis in whites and blacks and on assumptions of noncompliance with treatment among blacks.[11] Tuskegee was an attempt to demonstrate one aspect of a hypothesized difference between blacks and whites.

Minority women have frequently been the subject of unethical trials and interventions, often related to their reproductive health. The Tuskegee experiment is one example of the disregard for the health of women in the name of science. The men who were infected with syphilis continued to have relationships with their female partners, who were neither tested nor treated for syphilis. Even before Tuskegee, there was a long history of abuse of black women by physicians seeking to advance their knowledge. In the 1800s, for example, Dr. J. Marion Sims, the father of modern gynecology, specifically purchased black African slaves to perfect gynecological surgical procedures before he would try them on white women.[12]

Poor women have also been the target of unethical procedures. In 1929, the U.S. Supreme Court ruled that a poor, white, unwed mother could be sterilized without her explicit consent to prevent the reproduction of socially inadequate

offspring. Judge Oliver Wendell Holmes wrote that it was in the states' interest to sterilize women with hereditary defects. Subsequently, many states adopted compulsory sterilization laws. As late as the 1970s, there were reports of black and Puerto Rican women undergoing unnecessary hysterectomies and other forms of sterilization not only in the rural south but in prominent teaching hospitals in Boston and New York. These procedures were often done without the full informed consent of the woman. They were also often performed in public institutions by government employees.[13]

Women around the world have been the unwitting subjects of contraceptive technology and sterilization campaigns. Oral contraceptives, levonorgestrel (Norplant, Wyeth-Ayerst, Philadelphia, PA), and medroxyprogesterone acetate (Depo-Provera, Upjohn, Kalamazoo, MI) all were tested in developing countries, such as Bangladesh, Pakistan, and Mexico, where illiteracy is common and medical services are weak. Not only does this challenge the principle of informed consent, but women in communities of color often view the advances in contraceptive technology as efforts to commit genocide among their communities.[13–15]

Policies emanating out of the crack cocaine epidemic of the 1980s and 1990s led to disproportionate testing of pregnant black women for drugs, without their knowledge, even though white women are just as likely to abuse drugs and alcohol during pregnancy.[16] In one study of nonpregnant, primarily black patients using a public hospital, involuntary drug testing was built into the research design. Patients coming to a clinic were told their urine was being collected to assess infection, but in fact the researchers had the approval of their IRB to screen them for cocaine.[17] The authors justified this misrepresentation by arguing that the subjects would not tell the truth about their drug use. The researchers did not take into account the possible abuse the subjects would suffer or that the potential subjects most likely perceived they were not trusted by the investigators as legitimate reasons for withholding their drug habits.

Recently, the AIDS epidemic has taken a toll on communities of color. Women of color have the fastest growing rates of HIV infection in the United States.[18] The failure of public health and other efforts to curb the rate of HIV morbidity and mortality in communities of color to the same extent as in other populations is viewed with cynicism. Again, the concepts of genocide and government conspiracy are raised when addressing the sociopolitical aspects of this illness.[19,20] If researchers are to be successful in their efforts to include people of color, especially women of color, in AIDS clinical trials, they cannot ignore rumors of HIV as a government plot to kill off the black community along with homosexual men.

In communities of color, past injustices and exclusion from the health professions have created explicit feelings of distrust. Some patients are reticent to make decisions about diagnostic strategies and treatment without discussing the decision with family and friends.[21] Researchers seeking to include women of color in clinical trials must be aware of these feelings and willing to address them with the potential research participants.

Recent emphasis on disparities in health among different populations within the United States may elicit diverse responses among blacks and other minorities related to participation in clinical studies. For example, whereas cancer statistics show that African Americans have had worse disease outcomes than whites for the last 35 years and the gap is growing,[22] few studies have been developed to intervene and reduce the disparities. The current approaches to research addressing health disparities are too often designed without the input and participation of members of the communities to be recruited for the studies, either among the research team or as advisors. In addition to increasing participation of underrepresented groups in clinical trials, other important and related goals include increasing access to healthcare and other community resources, better training of healthcare providers to care for diverse populations in culturally competent ways, and educating more members from diverse communities to become researchers and healthcare providers.[1]

ISSUES AND BARRIERS

The barriers to recruitment of women from diverse populations into clinical trials can be classified into two categories: conceptual and structural. Studies that seek to include minority and other underrepresented populations may apply theoretical frameworks developed and tested

with members of the dominant culture. These frameworks may be invalid for more diverse groups of women. Other conceptual barriers include the lack of knowledge of clinical research, cultural differences from the Western biomedical model of health and treatment, the sociocultural context and experiences with research for various populations, and the support for the concept of altruism. This last concept places value on the actions of one individual to benefit a larger group or community. In research, this concept is applied when volunteers choose to participate in a study that may not directly benefit themselves but may benefit others with similar characteristics, conditions, or situations.

Common structural barriers include availability, accessibility, and acceptability.[23] Availability includes opportunities to participate in clinical trials in the places where potential participants live and conducting of study activities during hours compatible with participants' schedules, including weekend or late hours. Accessibility includes such issues as safety, transportation, child/family care, literacy, and language. Acceptability includes overcoming historical or personal negative experiences with and attitudes toward research and also that the study procedures or treatments fit the participants' lifestyles, preferences, and abilities for adherence. The ability of research staff to respond to questions and to treat the research participants with respect and cultural sensitivity also contributes to acceptability.[24–31]

The experience of the researchers in the CoEs in recruiting previously underrepresented women into clinical trials has reflected the same barriers as those identified in the literature. Examples of barriers faced in recruiting nonmajority women into clinical research were provided to us by several of the CoEs.

Many similar structural barriers, such as transportation and child care, were identified by most centers, but a few examples, based on regional differences, became apparent. At one CoE in the northern United States, for example, potential participants, especially older women, excluded themselves from participation because many spend the winter months in warmer climates. Transportation to the research site is a common problem experienced among all the CoEs. Many of the women rely on their husbands for transportation and prefer not to drive after dark. At many of the sites, women do not own a car and either fear public transportation or dislike the logistics that require several time-consuming transfers for a volunteer effort. Protocols that require fasting blood draws and, thus, morning appointments limit the participation of working women who cannot miss work for such activities. Finally, lack of child or family care options may make scheduling difficult, it not impossible.

Although structural and study design barriers are a concern, there are readily apparent options to reduce the impact of these concerns. Van pools, research sites in the target neighborhoods, and evening and weekend clinic hours are strategies to reduce the impact of these factors on study participation. Conceptual barriers, however, take more time and trust building to overcome. For example, many CoEs reported that a lack of perceived benefit was a major impediment to recruitment of women, particularly minority women, to clinical trials. At another CoE, women approached to participate in various studies expressed the belief that clinical studies are designed for men and not for women. Some women do not participate because they feel their partner, family, or friends would not approve. At another CoE, researchers found high levels of mistrust among minorities, particularly African Americans. Potential participants fear giving the healthcare provider too much control over their health. Individuals from minority populations have reported perceptions that the hospital or clinical center is always "taking from the community and not giving back." They identified feeling that the only time they hear from their medical center is when minorities are needed for a particular study.

Other groups of women who have been historically underrepresented in clinical studies are those who would be covered under the broadly constructed category of "special populations." This category includes women who have needs unique to their group that pose unusual barriers to optimal quality healthcare or who may have reason to mistrust the medical establishment. Examples of such groups include lesbian women, low-income women, women with disabilities, women for whom English is not the primary language, and women who are undocumented.

Although recruitment methods have been devised and tested to reach special populations, concern must continue to be exercised for the protection of these populations and to overcome barriers that prevent them from becoming involved

in clinical research. Failure to recruit from all parts of the diverse U.S. populations has been viewed and reviewed as a problem that raises both issues of equity and equitable access to clinical research and also scientific concerns about the generalizability of results of clinical research to populations not included in the studies. NIH has set standards for review of research proposals to include documentation of methods to reach women and minorities. Recruitment methods are under increasing scrutiny by IRBs to ensure more ethical recruitment and conduct of clinical studies. Recruitment methods for incorporating a broad range of potentially eligible participants are challenging and can be complicated by the need to recruit participants in short time frames and on limited budgets.

STRATEGIES TO ENHANCE PARTICIPATION IN CLINICAL TRIALS

The goal of strategies to enhance participation in clinical trials is to ensure that the research findings can be generalized appropriately to the diverse populations of women who are to be the recipients of future care. Thus, an understanding of each population to be included in the study is key. When investigators are outsiders to the communities identified for participant recruitment, gaining this understanding can be challenging. Thus, diversity within the research team as well as within the study participants should be considered when designing a study.

There is a range of effective strategies available for recruitment and retention to clinical studies. Strategies for recruitment may be based on established theoretical constructs and models, although existing models may not be valid for the populations traditionally underrepresented in research. Special challenges and strategies are necessary to recruit and retain culturally diverse women into research trials.[23] First, the culture and past experiences with the healthcare community of potential study participants must be understood. As mentioned previously, some groups may experience lower levels of healthcare than other populations as a result of institutionalized racism, restricted access to care, or economic constraints. Resources in the community may be lacking, and interactions with healthcare professionals may be negative. These factors, along with the historic mistreatment of minorities in research, have led to an overall suspicion of research and of those recruiting participants for studies on the part of some minority and other special populations of women.

Establishing community partnerships

Effective involvement of underrepresented groups of women in clinical trials requires a reconceptualization of the research process from one of recruitment of subjects to involvement of communities. In the former approach, researchers are the experts who seek community members as volunteers to a study with a previously established study purpose, design, and protocol, based on a belief that these volunteers will perceive sufficient benefit to agree to participate. In the alternative model, research takes place in communities and involves active participation of community members in the design and implementation of the research project.

Strategies to link with communities and their members need to be based on the nature of existing relationships between the investigators and the communities from which participation is sought. Investigators may identify key informants and leaders within the community to serve as liaisons between the investigators and potential participants, either through a formal structure, such as an advisory board to the study, or through less formal contacts. Investigators in clinical trials may be familiar with healthcare providers in a community, but they may be less familiar with other influential leaders, including religious leaders, community elders, or others, and must seek assistance from these leaders. Another strategy for community linkage involves becoming knowledgeable about the community by becoming an active member of the community in activities beyond the scope of the research, such as participating in community events or volunteering services. These approaches demonstrate respect for the contributions made by community partners as well as respect for the principle of doing no harm to the communities involved. They also inherently change the traditional roles and power relationships of investigator and subject, which can be threatening or confusing.

Principles for community-based research can help guide the development and implementation of clinical trials in communities previously underrepresented in research.[32] For example, one of

the CoE institutions developed, in partnership with community groups, the following statement[33]:

- Community partners should be involved at the earliest stages of the project, helping to define research objectives and having input into how the project will be organized.
- Community partners should have influence on project direction as well as ensuring that the original goals and methods of the project are adhered to appropriately.
- Research processes and outcomes should benefit the community. This might include hiring and training community members as research staff when appropriate, addressing community needs as identified by the community, and planning research that will build and enhance the assets of the community and its members.
- Community members should be part of the analysis and interpretation of data and should have input into how the results are disseminated. This means the opportunity to clarify the community's views about data interpretation, not censorship of data or dissemination of study results.
- Productive partnerships between researchers and community members should be encouraged to continue beyond the life of the specific research project. Such ongoing involvement increases the likelihood that research findings will be incorporated into the community's health programs and thus provide the greatest possible benefit to the community from research.

Principles such as these undergird the community-based research conducted in CoEs. When such statements are available, they can provide a stimulus for discussion and negotiation among academic investigators and community participants involved in specific projects.

CoE experiences suggest that some principles are more easily followed in some projects than in others. If the clinical trial design has been set at a national level, the national protocol should be reviewed with the planning groups so they are aware of the fixed parts of the research. Ideally, community participation would occur prior to the establishment of national or multisite protocols so that they can be informed by the cultural beliefs, practices, and perspectives of the multiple diverse populations.

Design study protocols based on knowledge of participants' life contexts

An examination of barriers to participation in clinical trials, discussed previously, highlights the importance of considering the pragmatic challenges to study participation faced by many women. Study procedures that are respectful of participants' time, need for transportation or child or elder care, and work schedules can promote both the recruitment and retention of underrepresented women.

Representation of diverse populations among research team

Ideally, the membership of the research team would include the same diversity as the population desired for participation in the clinical trial. Some participants may prefer to have interviews or other study procedures administered by someone of similar gender, race, or language or cultural group, whereas for others, it does not matter. However, providing a choice can enhance the comfort of participants with the study. Providing this diversity among the study team can be challenging, especially as women and minorities are underrepresented at present in the academic health sciences. To enhance diversity of both the study team and study participants, researchers may choose to link with investigators in regions of the country where certain populations or groups are more prevalent.

FUTURE CONSIDERATIONS

Clinical trials are now being designed specifically for women after decades of women's issues being understudied. The Women's Health Initiative (WHI),[34] the Breast Cancer Prevention Trial (BCPT),[35] and the Black Women's Health Study[36] are examples of large clinical trials that have developed and validated methods for finding, informing, and recruiting women into observational and prevention studies. Many challenges remain.

WHI and BCPT have stimulated the development of new statistical methods for global outcome monitoring in prevention trials. The methods for both monitoring and setting stopping rules for multiple beneficial and adverse outcomes will remain a challenge in prevention trials, and premature closure may preclude the

study of late beneficial or adverse effects. The BCPT presented an unusual challenge in that the pursuit of women at high risk for breast cancer resulted in a low-risk group for cardiovascular disease (CVD), and the CVD end point was not met. In addition, the unblinding of the BCPT trial for the highly statistically significant breast cancer end point will preclude a precise definition of the late effects, such as endometrial cancers. These same studies, though, have defined quality of life measures, critical to the life context of many women, as an integral component for clinical prevention trials.

Challenges to recruiting a sample of participants more representative of our diverse society will continue. Consent forms can be problematic. In spite of the new model consent form developed by the National Cancer Institute and Office of Protection of Research Rights, the consent form for Study of Tamoxifen and Raloxifene (STAR),[37] the second breast cancer prevention trial, is over eight pages long and requires 10th grade reading skills. In addition, prevention trials have not successfully recruited women who are not receiving regular preventive services, and this limitation will affect the generalizability of the results of these studies. Racial disparities are present in many clinical trials. Because gender and racial participation is essential for the development of knowledge related to efficacy of treatment, significant steps must be taken to remedy this situation. Large-scale educational efforts are needed, and many are underway to reach all communities with information about the design and conduct of clinical research and the importance of involvement of members of all communities. The CoEs can play a pivotal role by educating and advocating for gender equity in research.

Another long-term need is to erase the gender, race, and class separation between academic investigators and minority and underserved communities. This will be achieved only through concerted efforts to recruit and train more underrepresented groups for entry into academia and interventions to train clinicians and increase their skills in providing culturally competent services.

When diverse populations are included in clinical trials, such differences need to be honored during data analysis and interpretation. The NIH Revitalization Act of 1993 stated that women and minorities must be included in research, especially clinical trials, and that cost was not an acceptable reason for their exclusion. Additionally, analyses were to be conducted for gender differences. The General Accounting Office of Congress recently analyzed the performance, for fiscal year 1997, of the NIH in implementing these requirements. It found that although women have been included increasingly in clinical trials, women who are members of minority groups were not represented in proportions equal to their presence in the general population; 79.5% of women in extramural phase III studies of the NIH were Caucasian. The rest were African American (11.6%), Hispanic (4.4%), Asian/Pacific Islander (2.0%), and American Indian/Alaska Native (1.3%). When all extramural studies were examined, 52.7% of women participants were Caucasian, and whereas African American and Asian/Pacific Islander women were well represented (17.2% and 15.4%, respectively), Hispanic and American Indian/Alaska Native women were underrepresented (7.7% and 1.1%, respectively). Further, there has been limited progress in ensuring that analysis of study results by sex has occurred.[38] This report suggests that there is still progress to be made in recruiting women from diverse communities into research and even greater need to focus on making the results of clinical research applicable to historically underrepresented groups. Recruitment into clinical trials is only a beginning step, which must be followed by attention to identifying and understanding the variation in responses to interventions associated with gender, racial and ethnic heritage, age, and socioeconomic status.

In summary, there is an obvious need to increase the participation of minority and underrepresented women in clinical trials. To succeed, we have to understand the cultural contexts of diverse populations, as well as the barriers to participation and retention. Special strategies will be needed to achieve our objectives and provide scientific knowledge that is applicable to all. The goals of the CoE program include support for the development of leadership in women, especially those from underrepresented groups, in academic health science disciplines. Additionally, linkage of programs of research, education, community outreach, and clinical programs provides a model that will inform and improve the process of clinical

research, the inclusion of underrepresented groups in clinical trials, and the translation of research findings into healthcare.

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